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Sarcomas

Brain Metastases from Adult Sarcoma: Prognostic Factors and Impact of Treatment. A Retrospective Analysis from the French Sarcoma Group (GSF/GETO)

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Sarcoma • Brain metastases • Prognostic factors • French Sarcoma Group

Abstract

Background. Brain metastases (BM) from adult soft tissue or bone sarcomas are rare, and sparse data exist on their prognostic factors and management.

Subjects, Materials and Methods. A retrospective study was conducted in 15 centers of the French Sarcoma Group, plus one Canadian and one Swiss center, to report on clinical, histological, and treatment characteristics and to identify predictive factors of outcome.

Results. Between 1992 and 2012, 246 patients with a median age of 50 years (range: 16–86) were managed for BM. BM included 221 cerebral and cerebellar metastases and 40 cases of meningeal sarcomatosis. The most frequent histopathological subtype was leiomyosarcoma (18.7%). Histological grade was high in 118 (48%) cases. Surgery of BM was carried out for 38 (15.5%) patients. Radiotherapy and chemotherapy were administered in 168 (68.3%) and 91 (37.0%) patients, respectively. Irrespective of treatment modality, BM were controlled in 113 patients (45.9%), including 31 partial responses (12.6%) and 18 complete responses (7.3%). The median overall survival from diagnosis of brain metastasis was 2.7 months (range: 0–133). In the multivariate analysis, the following parameters influenced overall survival: chemotherapy (hazard ratio [HR] = 0.38; 95% confidence interval [CI]: 0.26–0.48), surgery (HR = 0.40; 95% CI: 0.22–0.72), stereotactic radiotherapy (HR = 0.41; 95% CI: 0.19–0.90), whole-brain radiotherapy (HR = 0.51; 95% CI: 0.35–0.76), and grade (HR = 0.65; 95% CI: 0.43–0.98).

Conclusion. BM of sarcomas are rare and associated with a dismal outcome. Multidisciplinary management with chemotherapy, radiation therapy, and surgery is associated with a better survival.

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Implications for Practice: The incidence of brain and meningeal metastasis in bone and soft tissue sarcomas is estimated between 1% and 8%. Published data are derived from small retrospective case series, often in the pediatric population. A prognostic index is important to guide both clinical decision-making and outcomes research, but one such is lacking for adult sarcoma patients with brain metastases. The current study describes brain metastasis in a large cohort of sarcoma patients. This study, conducted within the French Sarcoma Group, describes the natural history of sarcoma brain metastasis and enables the proposal of strategic recommendations for subsequent clinical trials and for the management of such patients.

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Introduction

Patients with cancer will develop brain metastases (BM) with an incidence between 10% and 30% [1]. The incidence of brain and meningeal metastasis in bone and soft tissue sarcomas (STS) is much lower, with estimates of 1%–8% [2–6]. Published data are derived from small retrospective case series, often in the pediatric population.

BM involvement in sarcoma is considered of unfavorable prognosis, but highly variable median survival rates are reported according to the studies [3–5, 7].

Depending on their anatomic location, size, and number, neurosurgical resection is reported to be the cornerstone of the management of sarcoma BM [2, 8, 9]. Radiation therapy has been used with little success. Systemic therapy has been used for patients with advanced/unresectable disease and in the palliative setting [10]. The clinical benefit of multimodal management of sarcoma BM is unknown, although there is evidence in BM of other solid tumors [11–15]. Therefore, the optimal management of sarcoma BM patients remains to be established with larger series of patients.

Here, we report the largest study to our knowledge describing BM in sarcoma patients. This study, conducted within the French Sarcoma Group (GSF/GETO), describes the natural history of sarcoma BM and enables the proposal of strategic recommendations for the management of such patients and for subsequent clinical trials.

Subjects, Materials, and Methods

Study Design

This retrospective study was approved by the multi-institutional review board of the French Sarcoma Clinical Reference Network NETSARC (website: http://www.netsarc.org). The study was conducted in 15 centers of the French Sarcoma Group (GSF/GETO), plus one Canadian and one Swiss center. Data were retrieved from the medical records of adult bone and soft tissue sarcoma patients with cerebral or meningeal metastases treated between 1992 and 2012.

Data Collection

The following information was collected: age at diagnosis, gender, symptoms at diagnosis, primary tumor characteristics (anatomic location, size, histological type, grade), date and location of first metastasis, time to brain metastasis, BM characteristics (number, location [cerebral and/or cerebellar and/or meningeal sarcomatosis], symptoms), performance status (PS) at BM diagnosis, management of BM, and outcomes. Systematic review was performed by expert pathologists of the GSF/GETO with histology established according to the World Health Organization Classification of Tumors [16]. Grade was determined as previously described according to the Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grading system [17]. Patients were treated at the discretion of their physician within the national sarcoma reference network. The effectiveness of the different therapies was assessed by each physician according to the standards applied at the time of the management of the patient. Response rates were defined according to RECIST.

Patient characteristics of long survivors were described. Long survivors were defined as patients with overall survival (OS) greater than 2 years.

Statistical Analysis

Classical methods of descriptive statistics were used for cohort description. Differences between groups were evaluated by the chi-square test or Fisher's exact test for categorical variables and Student's *t* test or Mann-Whitney *U* test for continuous variables.

OS was defined as the time from the date of diagnosis of BM until death of any cause. Surviving patients were censored at the last follow-up date. Progression-free survival (PFS) was defined as the time from the date of diagnosis of BM until date of progression or death of any cause, whichever came first. Time to brain metastasis (TBM) was defined as the time between the date of diagnosis of primary tumor and the date of diagnosis of BM. Surviving patients without disease progression were censored at date of the last follow-up. Survival curves were drawn with the Kaplan-Meier method and compared with the log-rank test. Univariate and multivariate analysis (Cox proportional hazards model) was used to identify potential predictive factors and to calculate hazard ratios (HR) with 95% confidence intervals (CI).

The following variables were examined in univariate analyses of OS and PFS: age, gender, PS, grade, TBM, anatomic location (cerebral and cerebellar metastases vs. meningeal sarcomatosis), number of BM (unique vs. multiple), surgery, chemotherapy, and radiotherapy. All variables were included in the multivariate analysis, and a backward selection was used to obtain the final model with most informative variables. All *p* values were two-sided and considered significant when $<.05$. All analyses were performed using SAS software version 9.3 (SAS Institute, Cary, NC).

Results

Patients and Disease Characteristics

Between 1992 and 2012, 246 patients were treated for BM in 15 centers of the GSF/GETO and one Canadian and one Swiss center. Patient characteristics are summarized in Table 1: 139 males (56.5%) and 107 females (43.5%) with a median age of 50 years (range: 16–86) were included. Median time between diagnosis of sarcoma and occurrence of BM was 18 months (range: 0–215), whereas it was only 9 months (range: 0–110) after occurrence of other metastases (pulmonary, liver, and bone metastases in 72.8%, 12.6%, and 23.2%, respectively). Most commonly, BM occurred after metastatic evolution at other sites. Only 54 patients (21.9%) with BM revealed metastatic evolution or were synchronous of other metastases. Patients had a median number of one chemotherapy line (range: 0–7) prior to diagnosis of BM.

Treatment (Table 2)

Surgery was performed in a minority of patients ($n = 38$, 15.5%), used both in cases of solitary BM lesions ($n = 19$, 7.7%) or with multiple BM lesions ($n = 19$, 7.7%). Among operated patients, complete resection was achieved in 10 of 38 patients (26.3%).

Table 1. Characteristics of overall population and long survivors

Characteristics	Overall population, *n* = 246, *n* (%)	Long survivors, *n* = 17, *n* (%)
Age, years		
Median	50	31
Range, min–max	16–86	17–65
Sex		
Female	107 (43.5)	7 (41.2)
Male	139 (56.5)	10 (58.8)
Primary tumor localization		
Limb	126 (51)	6 (35.3)
Trunk	43 (18)	4 (23.5)
Retroperitoneal	15 (6)	4 (23.5)
Uterus	15 (6)	1 (5.9)
Others	45 (19)	2 (11.8)
Initial tumor size, cm		
Median	9	6.5
Range, min–max	1–36	4–16
<6	31 (12.6)	2 (11.8)
6–10	72 (29.2)	5 (29.4)
>10	54 (22)	1 (5.9)
MD	89 (36.2)	9 (52.9)
Type		
Bone sarcoma	44 (18)	3 (17.6)
Soft tissue sarcoma	202 (82)	14 (82.4)
Histology		
Leiomyosarcoma	46 (18.7)	4 (23.5)
Ewing/primitive neuroectodermal tumor	30 (12.2)	3 (17.6)
Liposarcoma	19 (7.7)	0 (0)
Alveolar soft-part sarcoma	14 (5.7)	3 (17.6)
Osteosarcoma	14 (5.7)	0 (0)
Rhabdomyosarcoma	14 (5.7)	1 (5.9)
Angiosarcoma	14 (5.7)	0 (0)
Synovialosarcoma	13 (5.3)	2 (11.8)
Other sarcomas	82 (33.3)	4 (23.5)
Grade		
1	7 (2.8)	2 (11.8)
2	41 (16.7)	4 (23.5)
3	118 (48)	4 (23.5)
MD	80 (35.5)	7 (41.2)
TBM, months		
Median	18	73
Range, min–max	0–215	0–204
Interval between other metastases and BM, months		
Median	9	10
Range, min–max	0–110	0–88
Performance status		
0–2	120 (48.8)	13 (76.5)
3–4	60 (24.4)	0 (0)
MD	66 (26.8)	4 (23.5)

(continued)

Table 1. (continued)

Characteristics	Overall population, $n = 246$, n (%)	Long survivors, $n = 17$, n (%)
Symptoms		
Hemiplegia	54 (22)	1 (5.9)
Cranial nerve palsy	30 (12.2)	1 (5.9)
Headache	28 (11.4)	4 (23.5)
Nausea	23 (9.3)	1 (5.9)
Chance finding	23 (9.3)	3 (17.6)
Convulsion	18 (7.3)	2 (11.8)
Dizziness	9 (3.7)	1 (5.9)
Other	45 (18.3)	4 (23.5)
Localization in brain		
Cerebral or cerebellar	221 (89.8)	14 (82.4)
Meningeal sarcomatosis	40 (12.3)	4 (23.5)
Number of metastasis in brain		
1	87 (35.4)	9 (52.9)
Cerebral	73 (29.7)	7 (41.2)
Cerebellar	7 (2.8)	1 (5.9)
Meningeal sarcomatosis	7 (2.8)	1 (5.9)
2–5	88 (39.8)	6 (35.3)
>5	46 (20.8)	2 (11.8)
Other sites of metastasis		
Lung	179 (72.8)	12 (70.6)
Liver	31 (12.6)	1 (5.9)
Bone	57 (23.2)	4 (23.5)
Others	71 (28.9)	2 (11.8)

Abbreviations: BM, brain metastases; MD, missing data; TBM, time to brain metastasis.

Radiotherapy was used in the postoperative setting ($n = 22$, 8.9%), as a single modality ($n = 141$, 57.3%), or associated with sequential chemotherapy ($n = 63$, 25.6%).

Chemotherapy for BM was carried out in 91 patients (37.0%), with a median of one treatment line (range 1–2). Chemotherapy was administered in the postoperative setting ($n = 22$, 8.9%) or was associated with sequential radiotherapy ($n = 63$, 25.6%). BM were controlled in 66 patients (26.8%), including 11 complete responses (CR; 4.5%) and 20 partial responses (PR; 8.1%).

Eleven patients (4.5%) were treated with targeted therapy, namely sorafenib ($n = 5$), sunitinib ($n = 5$), and imatinib ($n = 1$).

Finally, palliative care alone was given in 46 (18.7%) patients.

Treatment Outcomes

Irrespective of treatment modality, BM were controlled in 113 patients (45.9%), including 31 partial (12.6%) and 18 complete (7.3%) responses, and 64 patients (26.0%) with stable disease (SD). Disease progression and no evaluable status were observed in 120 (48.8%) and 13 (5.3%) patients, respectively (Table 3).

At the time of analysis, 196 patients (79.7%) had died (disease-specific mortality: 175 patients; 71.1%), 30 patients (12.2%) were alive, and 20 (8.1%) were lost to follow-up.

Median OS from diagnosis of BM was 2.7 months (0–133; Fig. 1). Figure 2 shows median OS according to the response. On multivariate analysis, the following parameters influenced OS: chemotherapy (HR = 0.38; 95% CI: 0.26–0.48; $p < .0001$), surgery (HR = 0.40; 95% CI: 0.22–0.72; $p = .003$), stereotactic radiotherapy (HR = 0.41; 95% CI: 0.19–0.90; $p = .008$), whole-brain radiotherapy (WBRT; HR = 0.51; 95% CI: 0.35–0.76; $p = .003$), and histopathological grade (HR = 0.65; 95% CI: 0.43–0.98; $p = .035$; Table 4). The Eastern Cooperative Oncology Group (ECOG) performance status was excluded from this analysis because of missing data for a large number of patients (66 patients; 26.8%).

Long-Term Survivors

Patient characteristics of long-term survivors are summarized in Table 1.

Among the 246 patients, 17 (6.9%) patients (10 men and 7 women) with a median age of 31 years (range: 17–65) had an OS greater than 2 years. The primary tumor localization was the limb in six cases, trunk in four cases, retroperitoneum in four cases, and other sites in three cases. The median size of the primary tumor was 6.5 cm (range: 4–16). Histological subtypes included leiomyosarcoma ($n = 4$), Ewing sarcoma/peripheral primitive neuroectodermal tumor ($n = 3$), alveolar soft-part sarcoma ($n = 3$), synovial sarcoma ($n = 2$), and others ($n = 5$). Pathological grades were low, intermediate, high, and unknown in two, four, four, and seven patients, respectively. BM included 14 cerebral and cerebellar metastases and 4 cases

Table 2. Management modalities

Management modalities	Overall population, *n* = 246, *n* (%)	Long survivors, *n* = 17, *n* (%)
Surgery	38 (15.5)	7 (41.2)
Solitary lesion	19 (7.7)	4 (23.5)
Multiple lesion	19 (7.7)	2 (11.8)
MD	2 (0.9)	1 (5.9)
Median OS, months	15.1	
Range, min–max	6.9–19.9	
Radiotherapy	163 (66.3)	13 (76.5)
WBRT	144 (58.5)	10 (58.8)
Median OS, months	2.4	
Range, min–max	1.7–3.7	
Stereotactic	24 (9.8)	3 (17.6)
Median OS, months	10.2	
Range, min–max	5.6–19.9	
Exclusive	141 (57.3)	2 (11.8)
Sequential	63 (25.6)	4 (23.5)
Chemotherapy	91 (37)	11 (64.7)
Median line	1	1
Range, min–max	1–2	1–2
Median OS, months	7.7	
Range, min–max	6.2–11.8	
Combination regimen	38 (14.5)	8 (47.1)
Drugs		
Doxorubicin	23 (9.3)	5 (29.4)
Ifosfamide	22 (8.9)	7 (41.2)
Etoposide	20 (8.1)	3 (17.6)
Trabectedin	11 (4.5)	2 (11.8)
Platinum agents	10 (4)	3 (17.6)
Targeted therapy	11 (4.5)	1 (5.9)
Median OS, months	15.5	
Range, min–max	1.7–/	
Sorafenib	5 (2)	
Sunitinib	5 (2)	
Imatinib	1 (0.4)	1 (5.9)
BSC alone	46	0 (0)
Median OS, months	0.8	
Range, min–max	0.6–1.4	

Abbreviations: BSC, best supportive care; MD, missing data; OS, overall survival; WBRT, whole-brain radiotherapy.

of meningeal sarcomatosis. Among those, nine patients presented with solitary BM metastasis. Median TBM was 73 months (range: 0–204). Surgery and irradiation of BM were carried out for 7 (41.2%) and 13 cases (76.5%), respectively. Eleven patients (64.7%) received cytotoxic chemotherapy. CR, PR, and SD were observed in nine, three, and five patients respectively. Nine patients were dead at the end of follow-up, and among them, eight were dead from the evolution of their sarcoma and one without specified cause. Median OS from diagnosis of BM was 47 months (range: 24–133).

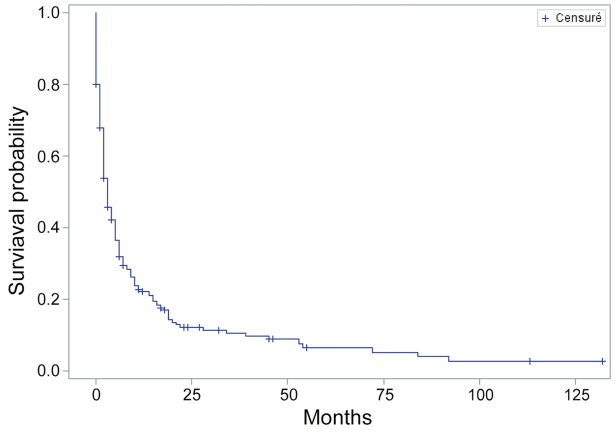

Figure 1. Overall survival of the brain metastases cohort.

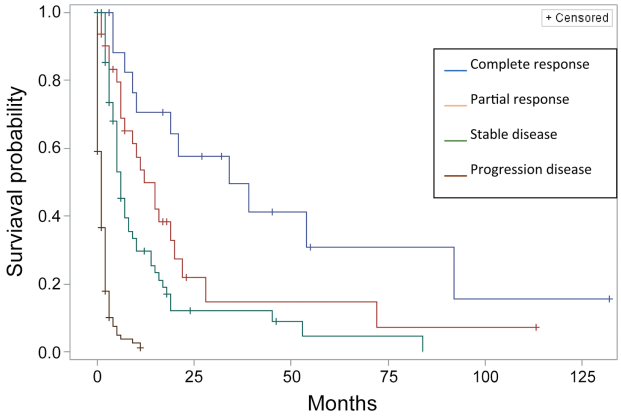

Figure 2. Overall survival of the brain metastases cohort according to response.

Discussion

BM from sarcoma is very rare. Espat et al. have evaluated a total of 3,829 STS patients, of whom 40 patients presented or developed BM, accounting for <1% of their overall cohort [6].

With a cohort of 246 patients, our collaborative study of the FSG is the largest series published to date on adult sarcoma BM patients [18]. This large retrospective study provides a precise description of histological subtype associated with BM relapse. BM from alveolar soft tissue sarcoma is largely reported in literature, but our study shows that BM are associated with more common histological subtypes. Leiomyosarcoma and liposarcoma represent 18% and 7%, respectively, of sarcoma associated with BM; this finding is comparable with the data from the Espat study [6]. We found that Ewing sarcoma and osteosarcomas represent 12% and 6%, respectively, of sarcoma with BM. BM occurrence for these subtypes have previously been reported between 32% and 56% [19–22].

Sarcomas with BM are more likely high-grade sarcomas (Table 1). Several studies have already described this association between grade and BM relapse [17, 23–27].

TBM relapse appears a late event in the natural history of sarcoma. In the literature, the range of TBM is estimated between 20 and 30 months (18 months in our cohort) [4, 8, 22, 28]. In most cases, patients developed BM after diagnosis of other metastases (pulmonary, liver, and bone metastases in 72.8%, 12.6%, and 23.2%, respectively, in our cohort) [6, 9, 29, 30].

Table 3. Treatment outcomes

Response and survival	Overall population, $n = 246$, n (%)	Long survivors, $n = 17$, n (%)
Response		
ORR	49 (19.9)	12 (70.6)
Complete response	18 (7.3)	9 (52.9)
Partial response	31 (12.6)	3 (17.6)
Stable disease	64 (26)	5 (29.4)
Progressive disease	120 (48.8)	0 (0)
Non-evaluable	13 (5.3)	0 (0)
Mortality	196 (79.7)	9 (52.9)
Disease-specific mortality	175 (71.1)	8 (47.1)
Brain evolution	111 (45.1)	8 (47.1)
Sarcoma evolution (other brain)	64 (26)	0 (0)
Complication of treatment	1 (0.4)	0 (0)
Other causes	1 (0.4)	0 (0)
Not specified	19 (7.7)	1 (5.9)
Alive	30 (12.2)	8 (47.1)
Lost to follow-up	20 (8.1)	0 (0)
Overall survival		
Median	2.7	47
Range, min–max	0–133	24–133

Abbreviation: ORR, objective response rate.

Table 4. Prognostic factors on overall survival (multivariate analysis)

Prognostic factors	HR (95% CI)	p value
Chemotherapy	0.38 (0.26–0.48)	<.0001
Surgery	0.40 (0.22–0.72)	.003
Stereotactic radiotherapy	0.41 (0.19–0.90)	.008
Whole-brain radiotherapy	0.51 (0.35–0.76)	.003
Grade	0.65 (0.43–0.98)	.035

Abbreviations: CI, confidence interval; HR, hazard ratio.

There is no standard for the treatment of BM from adult soft tissue or bone sarcomas, as for other cancers [11–15, 31]. Surgery and radiotherapy are often proposed [32]. In our study, surgery was performed in 15.5% of patients; radiotherapy was delivered in 66.3% of patients (WBRT and stereotactic radiotherapy were carried out in 58.5% and 9.8% of patients, respectively).

The role of local treatments in the context of metastatic spreading is difficult to establish without randomized study data. However, several studies seem to show a positive impact of surgery, particularly on lung metastases [33–39]. A meta-analysis of 18 publications reported OS 5-year rates of 25% for metastatic bone and 15% for metastatic soft tissue sarcomas, with corresponding 5-year rates of 34% and 25% for patients undergoing a first pulmonary metastasectomy [37]. Recently, a multicentric retrospective study of the French Sarcoma Group was conducted in oligometastatic sarcoma patients [38]. Of the 281 patients evaluated, 164 patients received local treatment for oligometastases. The median overall survivals were 45.3 months and 12.6 months, for the local treatment group and for no local treatment group, respectively (HR = 0.47; 95% CI: 0.29–0.78; $p < .001$). Authors conclude that local ablative treatment of oligometastatic diseases seems to improve the overall survival. Surgery yielded the most relevant results, but alternative approaches (radiofrequency ablation and radiotherapy) seemed to be promising [39]. Our results suggest that local treatments (neurosurgical resection, WBRT, stereotactic radiotherapy) improve the outcome of adult sarcoma patients with BM. However, the magnitude of this benefit appears limited. At the same time, our study suggests a significant positive correlation between median OS and the quality of response.

Chemotherapy remains the standard of care of advanced or metastatic sarcomas, but its impact appeared marginal in cases of BM. In our study, protocols were diverse but contained common drugs in sarcoma treatment: doxorubicin, ifosfamide, etoposide, trabectedin, and platinum agents. The surprise regarding chemotherapy is its place as a prognostic factor for OS (HR = 0.38; 95% CI: 0.26–0.48; $p < .0001$). Therefore, the question remains open: Which patients really benefit from chemotherapy? Probable selection criteria are the ECOG performance status and the histological subtype. Indeed, chemotherapy efficacy varies according to histological subtype, with a spectrum ranging from osteosarcoma and Ewing sarcomas (chemosensitive) to clear-cell sarcomas (chemoresistant) [40].

Seventeen (6.9%) patients (10 men and 7 women) with a median age of 31 years (range: 17–65) had an OS greater than 2 years. The long-term survivors seem younger than the entire cohort, 31 years versus 50 years, respectively. Furthermore, our study found possible differences of pathological grades (high-grade: 23.5% vs. 48%), ECOG PS ([0–2]: 76.5% vs. 48.8%), and TBM (73 vs. 18 months). However, it doesn't appear there are

differences concerning the incidence of histological subtypes. The long survivors are more widely treated by surgery and radiotherapy in comparison with the global population (41.2% vs. 15.5% and 76.5% vs. 66.3%, respectively). It should be noted that the long survivors subcohort had a greater percentage of solitary BM lesions (52.9% vs. 35.4%), in favor of a better prognosis of the oligometastatic disease. Indeed, 11 patients (64.7%) received cytotoxic agent, whereas chemotherapy was carried out in 37.0% of the global population.

Conclusion

Further questions remain open: What is the place of other treatment modalities such as surgery and radiotherapy and, notably, at which moment/sequence? Mono or polychemotherapy? What is the place of multimodality treatment? Even more fundamental: How to identify the BM sarcoma patients whose favorable overall prognosis would justify BM-specific treatment and who could ultimately benefit from such a treatment? Like melanoma, lung, or breast cancer, a prognostic index is important to guide both clinical decision-making and outcomes research, but one such is lacking for adult sarcoma patients with brain metastases [31].

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Disclosures

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For Further Reading:

Jennifer L. Pretz, Constance M. Barysauskas, Suzanne George et al. Localized Adult Ewing Sarcoma: Favorable Outcomes with Alternating Vincristine, Doxorubicin, Cyclophosphamide, and Ifosfamide, Etoposide (VDC/IE)-Based Multimodality Therapy. ***The Oncologist*** 2017;22:1265-1270.

Implications for Practice:

Ewing sarcoma (ES) is rare in adults. Treatment approaches for adults have been extrapolated from the pediatric experience, and there is a sense that adults fare less well than children. We reviewed treatment outcomes in adults with localized ES treated with cyclophosphamide, doxorubicin, and vincristine in alternation with ifosfamide and etoposide (VDC/IE) as part of multimodality therapy. Survival outcomes appear to be better than historical data for adults and similar to the excellent outcomes for children. These data help validate VDC/IE-based therapy as an appropriate treatment approach for this rare disease in adults.